Indolent Lymphomas

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Indolent non-Hodgkin lymphoma (iNHL), including follicular (FL) and marginal zone (MZL) lymphoma, now enjoy durable disease control with first-line immunochemotherapy, with a median overall survival (OS) of over 15 years in most series (Kahl and Yang 2016). However, iNHL is still widely considered incurable in most cases, and disease history remains characterized by a relapsing and remitting course, with each remission period shorter than the previous one, and OS and progression-free survival (PFS) decrease with each subsequent line of conventional therapy (Batlevi et al. 2020). Patients with unmet needs include approximately 20% of FL patients who experience disease progression within 24 months (POD24) after initial chemoimmunotherapy (with a 5-year OS of 48% (Casulo et al. 2015)—although it remains unclear how much this worse outcome is driven by misdiagnosed transformed follicular lymphoma (Freeman et al. 2019)); those who fail multiple regimens (5-year PFS of 23%) (Rivas-Delgado et al. 2019), have double refractory disease (Gopal et al. 2017) or experience relapse after autologous stem cell transplantation (ASCT) (Sesques et al. 2020). Although promising results were obtained with an immunomodulatory regimen combining anti-CD20 Moab and lenalidomide (Leonard et al. 2019; Morschhauser et al. 2019), most current approved therapies do not overcome incremental disease resistance, resulting in multiple lines of treatment with cumulative toxicity over a patient's lifetime. The autologous anti-CD19 chimeric antigen receptor T cell (CAR-T) therapies tisa-cel and axi-cel, which are now approved for patients with relapsed/refractory (r/r) large B cell lymphoma (LBCL), have also been tested in iNHL, with promising results.

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The ZUMA-5 phase 2 trial evaluated the efficacy and safety of axi-cel in 146 patients with r/r iNHL (FL: 124; MZL: 22) after at least two lines of therapy (Jacobson et al. 2020). Among the 104 patients available for the efficacy analysis (84 with FL and 20 with MZL), the overall response rate (ORR) was 92%, with 76% of patients obtaining complete remission (CR). In FL patients, the ORR was 94%, with a CR rate of 80%. Response rates were consistent among patients with high-risk features. With a median follow-up of 17.5 months, 64% of FL patients remained in response. The median duration of response (DoR), PFS, and OS were not reached (Gopal et al. 2017). The safety profile was manageable and appeared favourable in patients with FL compared with that previously reported in LBCL (Neelapu et al. 2017; Locke et al. 2019). Grade ≥ 3 adverse events (AEs) occurred in 126 patients (86%), most commonly neutropenia and infection. Fewer instances of any grade (78%) and high-grade (6%) cytokine release syndrome (CRS) were observed in the FL cohort. The onset of CRS was delayed compared with that seen in LBCL. The event was not resolved in only one patient, who ultimately died due to multiorgan failure (Jacobson et al. 2020). Fifty-six percent of patients experienced neurological events (NEs) of any grade; 15% had grade ≥ 3 events. Most NEs (67/70) resolved by the data cut-off time (Jacobson et al. 2020).

The same reliable results were seen with tisa-cel. In the phase 2 ELARA study, 98 adult patients with r/r FL within 6 months after second or later therapy or that relapsed after ASCT were enrolled (Fowler et al. 2020). Ninety-seven patients received tisa-cel, but 52 were evaluable for efficacy. Unlike the ZUMA-5 trial, bridging therapy was allowed, and 43% of patients received it. Thirty-four of 52 patients (65.4%) achieved a CR, with an ORR of 82.7%. With a median follow-up of 9.9 months, 69% of patients were still in response. Median DoR, PFS, and OS were not reached. Of the 97 patients evaluable for safety (median follow-up of 6.6 months), 69% experienced grade ≥ 3 AEs, most commonly neutropenia; 48% of patients had CRS, but none of them experienced a grade ≥ 3 AE. Any grade NEs occurred in 10% of patients; 2% had a grade ≥ 3 NE, and all recovered. No deaths seen were treatment-related (Fowler et al. 2020).

These preliminary data from the ELARA and ZUMA-5 trials suggest that anti-CD19 CAR-T cell treatment is effective in high-risk or extensively treated r/r iNHL, resulting in a high CR and ORR. Although the benefit/risk ratio seems highly favourable in high-risk FL patients, such as young, double refractory, relapse post-ASCT patients or those with POD24, longer follow-up times are needed to better define the potential for cure and the limited long-term toxicities, especially in view of the emergence of highly efficient competitive therapies, such as bispecific antibodies (Bannerji et al. 2020; Hutchings et al. 2020a,b; Assouline et al. 2020). Data remain scarce in MZL. Clearly, phase III randomized trials are mandatory to confirm the role of CAR-T cells in R/R in NHL, especially in POD24 patients.

Key Points

- Anti-CD19 CAR-T cell treatment achieves high CR and ORRs in extensively treated r/r FLs with an acceptable safety profile.
- The response appears durable, but the median follow-up time remains short.
- Data remain scarce in MZL.
- Phase 3 randomized trials are mandatory to confirm the role of CAR-T cells in r/r iNHL, especially in POD24 patients.

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